

**40 CFR Parts 795 and 799****[OPTS-42048D; FR 3209-5]****Hydroquinone; Final Test Standards and Reporting Requirements****AGENCY:** Environmental Protection Agency (EPA).**ACTION:** Final rule.

**SUMMARY:** On December 30, 1985, EPA issued a final test rule establishing testing requirements under section 4(a) of the Toxic Substances Control Act (TSCA) for manufacturers and processors of hydroquinone (CAS No. 123-31-9). At that time, EPA also proposed that certain TSCA test guidelines and industry-submitted protocols be utilized as the test standards for the required studies and that test data be submitted within specified time frames. EPA has reviewed public comments on the proposal and has decided to promulgate a final rule that specifies certain of these guidelines, protocols, and schedules as the test standards and reporting requirements for the testing of hydroquinone.

**DATES:** In accordance with 40 CFR 23.5, this rule shall be promulgated for purposes of judicial review at 1 p.m. eastern ["daylight" or "standard" as appropriate] time on June 11, 1987. This rule shall become effective on July 13, 1987.

**FOR FURTHER INFORMATION CONTACT:** Edward A. Klein, Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Rm. E-543, 401 M St. SW., Washington, DC 20460. (202) 554-1404.

**SUPPLEMENTARY INFORMATION:** In the Federal Register of December 30, 1985 (50 FR 53145), EPA issued a final Phase I rule under section 4(a) of TSCA to require toxicity testing of hydroquinone to evaluate hydroquinone's toxicokinetics and to determine its potential to produce nervous system, reproductive, and developmental toxicity (teratogenic effects). The Agency is now promulgating a final Phase II rule specifying the test standards and reporting requirements for this testing. This test standards rule for hydroquinone is being promulgated under 40 CFR 799.2200.

**I. Background**

In the Federal Register of December 30, 1985, EPA issued a Phase I final rule pursuant to TSCA section 4 that established testing requirements for manufacturers and processors of hydroquinone. This Phase I rule specified the following testing requirements for hydroquinone: (1) Toxicokinetics; (2) reproductive effects; (3) developmental toxicity; and (4) nervous system effects.

As described in the Hydroquinone Proposed Testing Standards (50 FR 53160) and in a previous notice (50 FR 20652; May 17, 1985) EPA reviewed the method for development of test rules and, to expedite the section 4 rulemaking process, decided to utilize a single-phase approach for most rulemakings. With regard to the section 4 rulemaking for hydroquinone, EPA proposed applicable TSCA test guidelines and EPA-approved industry protocols as test standards. At the same time as the hydroquinone Phase I final test rule was being issued, TSCA test guidelines and EPA-approved industry protocols were available for all the testing requirements included in the Phase I final rule. After publication of the proposed hydroquinone test standards on December 30, 1985, a 45-day comment period was provided to allow the public, including the manufacturers and processors subject to the Phase I rule, to comment on the use of the TSCA guidelines and industry protocols.

Because EPA proposed applicable TSCA test guidelines and industry-submitted protocols as the test standards for the studies required by the hydroquinone Phase I final rule, persons subject to the rule, i.e., manufacturers

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and processors of hydroquinone, were not required to submit proposed study plans and schedules for each of the required studies. Persons subject to the rule, however, were still required to submit notices of intent to test or exemption applications in accordance with 40 CFR 790.25. Once the final test standards are promulgated, persons who have notified EPA of their intent to test must submit study plans (which adhere to the promulgated test standards) no later than 45 days before the initiation of each required test. The responsibilities of processors of hydroquinone for testing or exemptions from testing responsibilities were discussed in the hydroquinone Phase I final rule (50 FR 53145).

On June 15, 1983 and prior to the Agency's issuance of the hydroquinone Phase I Proposed Rule, the Eastman Kodak Company notified EPA by letter (Ref. 1) of their intent to conduct voluntary toxicokinetic, mutagenicity, and teratology tests with hydroquinone and submitted the protocols for these studies to the Agency for review. Kodak also submitted protocols for additional confirmatory teratology and reproductive effects studies which they indicated would be conducted under their voluntary plan only after a joint evaluation by Kodak and EPA scientists of any additional EPA health concerns remaining after the initial testing. At the time of the submission of this voluntary testing package, EPA was in the process of concluding its review of the health and environmental effects testing needs for hydroquinone. While the Agency approved several of the Kodak testing protocols, EPA did not accept Kodak's voluntary testing program because the Agency was in the process of issuing a proposed test rule (49 FR 438; January 4, 1984) for hydroquinone that would require more complete health and environmental testing of the chemical.

Kodak, however, initiated its testing program and, sometime later, the manufacturers and importers of hydroquinone formed the Hydroquinone Panel, represented by the Chemical Manufacturers Association. Kodak, in concert with the Panel, is continuing its testing efforts. As part of its comments (Ref. 2) to the proposed Hydroquinone Test Standards (50 FR 53160) the Panel has notified EPA of its intent to sponsor the testing required in the final Phase I test rule for hydroquinone.

After review of the public comments, EPA is now promulgating a final Phase II rule adopting (with appropriate revisions based on public comment) formal test standards under which the manufacturers and processors of

hydroquinone must conduct the health effects studies contained in the Phase I test rule for hydroquinone. These standards were proposed in the December 30, 1985 notice (50 FR 53160). These standards and requirements reflect the Agency's evaluation of comments received on the proposed test standards rule.

## II. Proposed Phase II Test Rule

### A. Proposed Test Standards

The final Phase I rule for hydroquinone required testing for toxicokinetics, developmental toxicity, reproductive effects, and nervous system effects.

The Agency proposed that the toxicokinetic guideline under 40 CFR 798.7650 now 40 CFR 795.235, which was contained in the proposed Phase II test standard rule, be adopted as the test standard for the required toxicokinetic testing.

EPA proposed that the developmental toxicity testing be conducted according to the protocols entitled "Protocol for a Teratology Study of Hydroquinone in Rats" and "Protocol for a Teratology Study of Hydroquinone in Rabbits", submitted to EPA by the Eastman Kodak Company on June 15, 1983 (Ref. 1) and that these industry-submitted protocols be adopted as the test standard for the required developmental toxicity testing.

EPA also proposed that the reproductive effects testing be conducted according to the protocol entitled "Protocol for a Two-Generation Reproduction Study in the Rat" submitted to EPA on June 15, 1983 (Ref. 1) and that this industry-submitted protocol be adopted as the test standard for the required reproductive effects testing.

Finally, the Agency proposed that TSCA test guidelines 40 CFR 798.6050 and 798.6400, describing a functional observational battery and neuropathology, respectively, be adopted as the test standards for the required neurotoxicity testing of hydroquinone.

### B. Proposed Reporting Requirements

EPA proposed that all data developed under the Phase II rule be developed in accordance with the final TSCA Good Laboratory Practice (GLP) Standards, which appear at 40 CFR Part 792.

The Agency proposed the following specific reporting requirements:

1. The toxicokinetic tests shall be completed and the final results submitted to the Agency within 1 year of the effective date of the final Phase II test rule. Interim progress reports shall be provided quarterly.

2. The developmental toxicity tests shall be completed and the final results submitted to the Agency within 18 months of the effective date of the final Phase II test rule. Interim progress reports shall be provided quarterly.

3. The two-generation reproductive effects toxicity test shall be completed and final results submitted to the Agency within 29 months of the effective date of the final Phase II test rule. Interim progress reports shall be provided quarterly.

4. The neurotoxicity tests shall be completed and final results submitted to the Agency within 1 year of the effective date of the final Phase II test rule. Interim progress reports shall be provided quarterly.

## III. Response to Public Comments

EPA requested comments on the use of the TSCA test guidelines and Agency-approved industry protocols as the test standards for the required testing of hydroquinone and the proposed schedules for the required testing. The Agency received written comments from the Hydroquinone Panel (Ref. 2); however, a public meeting was not requested.

In keeping with the intent of this Phase II rule, which is to establish the test standards and the scheduling of those tests, the Agency is responding to those industry comments which are relevant to those issues. However, issues in the comments concerning the necessity for testing have been previously discussed in the proposed and final phase I rule and are therefore not discussed here. No comments relating to the test standards for the developmental toxicity and reproductive effects testing were received.

### A. Toxicokinetics

The hydroquinone Phase I final rule required skin and oral dosing studies, which will provide data regarding both the rate and extent of absorption of hydroquinone through the skin. In the proposed Phase II test standards rule, the Agency proposed a specific test standard in § 798.7650 recodified as § 795.235 in this rule to be followed when conducting the required oral and dermal testing of hydroquinone in rats.

With regard to the dermal studies, the CMA Hydroquinone Panel has commented that EPA should require an *in vitro* study of the kinetics of hydroquinone penetration through rat skin in place of the proposed *in vivo* rat skin absorption study. They argue that data on dermal penetration in the rat can be obtained in a more reliable, rapid, and cost-effective manner by an

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*in vitro* study and such a study would allow longer exposure periods and direct collection of quantitative data (Ref. 2).

Kodak supports their argument by citing a Kodak study of the percutaneous absorption of [ $^{14}\text{C}$ ] hydroquinone in dogs (Refs. 2 and 6). Kodak argues that because the dog study showed very slow skin penetration (about 1.1  $\mu\text{g}/\text{cm}^2/\text{hr}$ ), similar tests in rats would not provide enough penetration to characterize metabolites and would provide only data on the skin penetration rate of hydroquinone through rat skin. The Panel adds that if their suggested *in vitro* study establishes a high rate (higher than the low rate expected by the Panel) they then can conduct an *in vivo* study.

The CMA Hydroquinone Panel requested a meeting with the Agency to discuss these issues, and the meeting was held on September 4, 1986 (Ref. 3). After reviewing (Refs. 4, 5, and 8) the arguments presented by the Hydroquinone Panel (Refs. 1, 6, and 7), the Agency rejects the modification to the test standard as proposed by the Panel. This decision is based on the following reasons: (1) The Agency believes that the dermal penetration study, "Percutaneous Absorption of Hydroquinone in Beagle Dogs," upon which the Panel has based its prediction of limited skin penetration in rats, has serious deficiencies. Deficiencies, such as the failure of the study to account for large amounts of the hydroquinone administered to the test animals, make it impossible for the Agency to reasonably predict the behavior of hydroquinone applied to other test animals such as rats or to the skin of humans exposed to hydroquinone. (2) While the Panel has suggested that they would perform an *in vivo* test if their suggested *in vitro* study shows a "high" skin penetration rate, they have not stated what level of absorption in the *in vitro* study or other factors would dictate that the *in vivo* study should also be conducted.

#### B. Neurotoxicity

With regard to the neurotoxicity testing required by the hydroquinone Phase I final test rule, the Agency proposed that the functional observational battery and neuropathology be conducted in accordance with 40 CFR 798.6050 and 798.6400, respectively.

In its comments, CMA's Hydroquinone Panel proposed that the functional-observational battery and the neuropathology examinations be conducted sequentially on the same group of rats. They comment that in

conducting neurotoxicological evaluations, the best data would be expected from studies which integrate functional observations with microscopical observations. They add that a sequential study would also be the most cost-effective use of testing resources, would reduce the number of test animals, and would provide internal test controls. Critical analysis of any observed functional effects would be used to plan the pathologic examination.

The Panel suggested that the study be conducted by dosing the test animals at three levels and observing all the dosed animals as appropriate for the functional-observational battery. Neuropathology would then be conducted only on the high-dose group. No neuropathology would be conducted on animals receiving the lower doses, unless abnormal effects are observed during the study of the high-dose animals.

EPA believes that the functional-observational battery could indeed be carried out in conjunction with neuropathological assessment, and would spare committing additional animals to the toxicity evaluation. Neuropathological assessment should begin with the highest dose level and work downward until a no-observable-adverse-effects dose level is reached. According to the functional-observational battery testing guideline, the highest dose used should result in clear behavioral effects regardless of whether these are of a neural origin. Smaller doses are selected appropriately so as to provide information on the shape of the dose-response curve. The Agency agrees with the suggestion of a staged neuropathology examination, as described in the TSCA neuropathology test guidelines.

#### IV. Final Phase II Test Rule

##### A. Test Standards

The TSCA test guidelines for toxicokinetic studies in 40 CFR 795.235, the neurotoxicity testing in 40 CFR 798.6050 and 798.6400 and the industry-submitted protocols for developmental toxicity and reproductive effects testing shall be the test standards for the testing of hydroquinone required under 40 CFR 799.2200. The Agency believes that the conduct of the required studies in accordance with these test standards is necessary to assure that the results are reliable and adequate.

The revised guidelines for tests included in this Phase II rule, published in the Federal Register of May 20, 1987 (52 FR 19056), are adopted in the test standards for the testing of hydroquinone. EPA has responded to

comments concerning these guideline revisions and that response to comment document is contained in the record for this rulemaking (Ref. 9).

##### B. Reporting Requirements

The Agency is requiring that all data developed under this rule be reported in accordance with the TSCA Good Laboratory Practice Standards (40 CFR Part 792).

Test sponsors are required to submit individual study plans at least 45 days prior to the initiation of each study in accordance with 40 CFR 790.50.

The Agency is required by TSCA section 4(b)(1)(C) to specify the time period during which persons subject to a test rule must submit test data. On the basis of its experience with health effects testing, EPA is adopting the proposed schedule for the submission of final test results as the final Phase II rule schedule.

The Agency has revised the reporting requirement for the submission of interim progress reports for testing under section 4 of TSCA. Accordingly, the Agency now requires only 6-month interim progress reports on all studies for hydroquinone, as opposed to the quarterly reporting schedule contained in the proposed test standard rule.

TSCA section 14(b) governs Agency disclosure of all test data submitted pursuant to section 4 of TSCA. Upon receipt of data required by this rule, the Agency will publish a notice of receipt in the Federal Register as required by section 4(d).

##### C. Conditional Exemptions Granted

The final rule for test rule development and exemption procedures (40 CFR Part 790) indicates that, when certain conditions are met, exemption applicants will be notified by certified mail or in the final Phase II test rule for a given substance that they have received conditional exemptions from test rule requirements. The exemptions granted are conditional because they will be given based on the assumption that the test sponsors will complete the required testing according to the test standards and reporting requirements established in the final Phase II test rule for the given substance. TSCA section 4(c)(4)(B) provides that if an exemption is granted prospectively (that is, on the basis that one or more persons are developing test data, rather than on the basis of prior test data submissions), the Agency must terminate the exemption if the test sponsor has not complied with the test rule.

Because sponsors have indicated to EPA by letter or intent (Ref. 1) their

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agreement to sponsor all of the tests required for hydroquinone in the final Phase I test rule for this substance according to the test standards and reporting requirements established in this final Phase II test rule for hydroquinone, the Agency is hereby granting conditional exemptions to all exemption applicants for all of the testing required for hydroquinone in 40 CFR 799.2200.

#### D. Judicial Review

The promulgation date for the hydroquinone Phase I final rule was established as 1 p.m. eastern standard time on January 13, 1986 (50 FR 53145; December 30, 1985). EPA received no petitions for review of that Phase I final rule. Accordingly, any petition for judicial review of this Phase II final rule will be limited to a review of the test standards and reporting requirements for hydroquinone established in this rule.

#### E. Other Provisions

Section 4 findings, required testing, test substance specifications, persons required to test, enforcement provisions, and the economic analysis are presented in the final Phase I rule for hydroquinone (50 FR 53145).

#### V. Rulemaking Record

EPA has established a record for this rulemaking. [docket number (OPTS-42048D)]. This record includes basic information considered by the Agency in developing this rule, and appropriate Federal Register notices.

This record includes the following information:

##### A. Supporting Documentation

The supporting documentation for this rulemaking consists of the proposed and final Phase I test rules on hydroquinone and the proposed hydroquinone test standards rule.

##### B. References

- (1) Eastman Kodak Company. Protocols for a Voluntary Test Program on Hydroquinone. Submitted to Steven Newburg-Rinn, Chief, Test Rules Development Branch. (June 15, 1983).
- (2) Chemical Manufacturers Association. Comments on Hydroquinone: Proposed Testing Standards 50 FR 53160; December 30, 1985. Submitted by the Hydroquinone Program Panel of the Chemical Manufacturers Association. (February 13, 1986).
- (3) Meeting summary. CMA Hydroquinone Panel and EPA's Office of Toxic Substances. (September 4, 1986).
- (4) Memorandum USEPA. Charles Abernathy Ph.D., Health and Environmental Review Division, to Gary E. Timm, Existing

Chemicals Assessment Division. (June 20, 1986).

(5) Memorandum. USEPA. Charles Abernathy Ph.D., Health and Environmental Review Division, to David Price, Existing Chemicals Assessment Division. (November 17, 1986).

(6) Letter. Geraldine Cox, Chemical Manufacturers Association, to David Price, Existing Chemicals Assessment Division. In attachment, discussion of *in vitro* and *in vivo* testing for skin absorption. (October 2, 1986).

(7) Letter. Kathryn Rosica, Chemical Manufacturers Association, to Document Control Officer, USEPA. Suggested *in vitro* study protocol. (May 28, 1986).

(8) Document review. Review and evaluation of Eastman Kodak Study—"The Percutaneous Absorption of U-<sup>14</sup>C Hydroquinone in Beagle Dogs" by Research Evaluation Associates. (January 6, 1986).

(9) USEPA. "Response to Public Comments, Proposed Revision of TSCA Test Guidelines as published in 51 FR 1522 (January 14, 1986)". Test Rules Development Branch, Existing Chemicals Assessment Division, Office of Toxic Substances, Environmental Protection Agency, Washington, DC (January 1987).

The record is available for inspection from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays, in Rm. G-004, Northeast Mall, 401 M Street SW., Washington, DC 20460.

#### VI. Other Regulatory Requirements

##### A. Executive Order 12291

Under Executive Order 12291, EPA must judge whether a regulation is "major" and therefore subject to the requirements of a Regulatory Impact Analysis. This test rule is not major because it does not meet any of the criteria set forth in section 1(b) of the Order. The economic analysis of the testing of hydroquinone is discussed in the Phase I test rule (50 FR 53145; December 30, 1985).

This final Phase II test rule was submitted to the Office of Management and Budget (OMB) for review as required by Executive Order 12291. No comments were received.

##### B. Regulatory Flexibility Act

Under the Regulatory Flexibility Act, (15 U.S.C. 601 *et seq.*, Pub L. 96-354, September 19, 1980), EPA is certifying that this rule will not have a significant impact on a substantial number of small businesses for the following reasons:

- (1) There are not a substantial number of small businesses manufacturing hydroquinone.
- (2) Small processors are not expected to perform testing themselves, or to participate in the organization of the testing efforts.
- (3) Small processors will experience only very minor costs if any in securing exemption from testing requirements.

(4) Small processors are unlikely to be affected by reimbursement requirements, and any testing costs passed on to small processors through price increases will be small.

#### C. Paperwork Reduction Act

OMB has approved the information collection requirements contained in this final rule under the provisions of the Paperwork Reduction Act of 1980, 44 U.S.C. 3501 *et seq.*, and has assigned OMB control number 2070-0033. No public comments on these requirements were submitted to the Office of Information and Regulatory Affairs of OMB.

#### Lists of Subjects in 40 CFR Parts 795 and 799

Testing, Environmental protection, Hazardous substances, Chemicals, Recordkeeping and reporting requirements.

Dated: May 11, 1987.

J.A. Moore,

Assistant Administrator for Pesticides and Toxic Substances.

Therefore, Chapter I of 40 CFR is amended as follows:

#### PART 795—[AMENDED]

##### 1. In Part 795:

a. The authority citation for Part 795 continues to read as follows:

Authority: 15 U.S.C. 2603, 2611, 2625.

b. Section 795.235 is added, to read as follows:

##### § 795.235 Toxicokinetic Test.

(a) *Purpose.* These studies are designed to: (1) Determine the bioavailability of the test substance after dermal or oral treatment.

(2) Ascertain whether the metabolites of the test substance are similar after dermal (assuming significant penetration) and oral administration.

(3) Examine the effects of a multiple dosing regimen on the metabolism of the test substance after *per os* administration.

##### (b) *Definition of scope of study.*

Absorption toxicokinetics refers to the bioavailability, i.e., the rate and extent of absorption of the test substance, and metabolism and excretion rates of the test substance after absorption.

##### (c) *Test procedures—(1) Animal selection—(i) Species.*

The rat is the animal species of choice since it has been used extensively for absorption, metabolism, and toxicological studies.

(ii) *Rat strain.* Adult male and female Fischer 344 rats shall be used. At 7 to 9 weeks of age, the males should weigh 125 to 175 g and the females 110 to 150 g.

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The rats shall be purchased from a reputable dealer and identified with ear tags upon arrival. The animals shall be randomly selected for the testing groups, and no unhealthy animal is to be used for experimentation.

(iii) *Animal care.* (A) Animal care and housing should be in accordance with Department of Health, Education and Welfare Publication No. (NIH)-78-23, 1978. "Guidelines for the Care and Use of Laboratory Animals," or its equivalent.

(B) The animals shall be housed in environmentally controlled rooms with 10 to 15 air changes per hour. The rooms shall be maintained at a temperature of  $25 \pm 2^\circ\text{C}$  and humidity of  $50 \pm 10$  percent with a 12-hour light/dark cycle per day. The rats shall be kept in a quarantine facility for at least 7 days prior to use.

(C) During the acclimatization period, the rats shall be housed in polycarbonate cages on hardwood chip bedding. All animals shall be provided with certified feed and tap water *ad libitum*.

(iv) *Number of animals.* There shall be at least four animals of each sex in each experimental group.

(2) *Administration of test substance—*

(i) *Test substance.* Test substance of at least 99 percent purity, commercially available, should be used as the test substance. Since both nonradioactive and radioactive (uniformly  $^{14}\text{C}$ -labelled) test substances are to be used, they should be chromatographed separately and analyzed together, to ascertain purity and identity. The use of  $^{14}\text{C}$ -labelled test substance, diluted with unlabeled test substance, is required for all of the studies under this section, unless otherwise specified, as it will greatly increase the reliability and sensitivity of the quantitative assays and facilitate the identification of metabolites.

(ii) *Dosage and treatment.* (A) Two doses shall be used in studies under this section, a "low" dose and a "high" dose. When administered orally, the "high" dose level should ideally induce some overt toxicity, such as weight loss. The "low" dose level should not induce observable effects attributable to the test substance. If feasible, the same "high" and "low" doses should be administered orally and dermally.

(B) Oral dosing shall be accomplished by gavage after dissolving the test substance in a suitable vehicle. For dermal treatment, the doses shall be administered in a suitable solvent and applied at a volume adequate to deliver the prescribed doses. The backs of the rats should be shaved with an electric clipper one day before treatment. The dose should be applied with a

disposable micropipette on a specific area ( $2\text{ cm}^2$  for rats) on the shaven skin. The dosed areas shall be occluded with an aluminum foil patch which is secured in place with adhesive tape.

(iii) *Determination of test substance kinetics.* Each experimental group shall contain at least four rats of each sex for a total of eight rats.

(a) *Oral studies.* (1) Group A shall be dosed once *per os* with the low dose of the test substance.

(2) Group B shall be dosed once *per os* with the high dose of the test substance.

(3) For the oral studies, the rats shall be placed in individual metabolic cages to facilitate collection of urine and feces at 8, 24, 48, 72, and 96 hours following administration. The cages shall be cleaned at each time period to collect any metabolites that might adhere to the metabolic cages.

(B) *Dermal Studies.* (1) Group C shall be dosed once dermally with the low dose of test substance.

(2) Group D shall be dosed once dermally with the high dose of test substance.

(3)(i) For the dermal studies, the test substance shall be applied for 24 hours. Immediately after application, each animal shall be placed in a separate metabolic cage for excreta collection. At the time of removal of the aluminum foil, the occluded area shall be washed with an appropriate solvent (see below), to remove any test substance that may be on the skin surface and the wash solvent assayed for the amount of test substance recovered. At the termination of the experiments, each animal shall be sacrificed and the exposed skin area removed. The skin (or an appropriate section) shall be solubilized and assayed for the test substance and its metabolites.

(ii) Before initiation of the dermal studies, an initial washing efficiency experiment shall be conducted to assess the removal of the applied test substance by washing the exposed skin area with soap and water or organic solvents. Four rats, two of each sex, shall be lightly anesthetized and then test substance applied to a specified area. After application (5 to 10 minutes), the areas should be washed with soap and water (two rats) or ethanol and water (two rats). The amount recovered shall be determined to assess efficacy of test substance removal by washing of the skin.

(C) *Repeated dosing study group E.* Four rats (two of each sex) shall receive a series of single daily oral doses of nonradioactive test substance over a period of at least 14 days, followed at 24 hours after the last dose by a single oral

dose of  $^{14}\text{C}$ -labelled test substance. Each dose shall be at the low dose level.

(3) *Observation of animals—*(i) *Bioavailability—*(A) *Blood levels.* The levels of  $^{14}\text{C}$  shall be determined in whole blood, blood plasma, or blood serum at appropriate intervals from 1 to 96 hours after dosing rats in Groups A through E. Four rats (two of each sex) of each group shall be used for this purpose.

(B) *Urinary and fecal excretion.* The quantities of  $^{14}\text{C}$  excreted in the urine and feces by rats in groups A through E shall be determined at 8 hours, 24 hours, 48 hours, 72 hours, and 96 hours after dosing, and if necessary, daily thereafter until at least 90 percent of the applied dose has been excreted or until 7 days after dosing (whichever occurs first). Four animals (two of each sex) shall be used for these analyses.

(ii) *Biotransformation after oral and dermal dosing.* Appropriate qualitative and quantitative methods shall be used to assay the test substance and metabolites in the urine and fecal specimens collected from rat Groups A through D.

(iii) *Changes in Biotransformation.* Appropriate qualitative and quantitative assay methodology shall be used to compare the composition of  $^{14}\text{C}$ -labelled compounds in excreta collected at 14 and 48 hours after dosing rat Group A with those in the excreta collected at 24 and 48 hours after the  $^{14}\text{C}$ -labelled test substance dose in the repeated dose study (Group E).

(d) *Data and reporting—*(1) *Treatment of results.* Data should be summarized in tabular form.

(2) *Evaluation of results.* All observed results, quantitative or incidental, should be evaluated by an appropriate statistical method.

(3) *Test report.* In addition to the reporting requirements specified in the EPA Good Laboratory Practice Standards (40 CFR Part 792, Subpart J) the following specific information shall be reported:

(i) Specie(s) and strain(s) of laboratory animals.

(ii) Information on the degree (i.e., specific activity for a radiolabel) and site(s) of labeling of the test substance;

(iii) A full description of the sensitivity and precision of all procedures used to produce the data.

(iv) Percent absorption by oral and dermal routes of rats administered  $^{14}\text{C}$ -test substance.

(v) Quantity of isotope, together with percent recovery of administered dose in feces, urine, blood, and skin and skin washings (dermal study only for last two portions).

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(vi) Quantity and distribution of  $^{14}\text{C}$ -labelled test substance in various tissues, including bone, brain, fat, gonads, heart, kidney, liver, lung, muscle, spleen, and residual carcass.

(vii) Counting efficacy data shall be made available to the Agency upon request.

#### PART 799—[AMENDED]

##### 2. In Part 799:

a. The authority citation for Part 799 continues to read as follows:

Authority: 15 U.S.C. 2603, 2611, 2625.

b. By amending § 799.2200 by adding paragraphs (c)(1) (ii), (iii), (2) (ii), (iii), (3) (ii), (iii), (4) (ii), (iii), and (d) to read as follows:

#### § 799.2200 Hydroquinone.

(c) \* \* \*

(1) \* \* \*

(ii) *Test standard.* The toxicokinetic testing shall be conducted in accordance with § 795.235 of this chapter.

(iii) *Reporting requirements.* (A) The toxicokinetic tests shall be completed and the final results submitted to the Agency within 1 year of the effective date of the Phase II final test rule.

(B) A progress report shall be provided 6 months from the effective date of the final Phase II rule.

(2) \* \* \*

(ii) *Test standards.* The developmental toxicity testing shall be conducted according to the teratology study plans submitted to the EPA on June 15, 1983 (Eastman Kodak Company, 1983) and reviewed by the Agency as part of the study plan. Copies of the study plan are located in the public record for this test rule (Docket No. OPTS-42048D) and are available for inspection in the OPTS Reading Rm., G-004, Northeast Mall, 401 M. St., SW., Washington, DC 20460, from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays.

(iii) *Reporting requirements.* (A) The Developmental toxicity tests shall be completed and the final results submitted to the Agency within 18 months of the effective date of the final Phase II rule.

(B) Interim progress reports shall be provided at 6-month intervals beginning 6 months from the effective date of the final Phase II rule.

(3) \* \* \*

(ii) *Test standard.* The reproductive effects testing shall be conducted according to the two generation reproduction unit of the study plan, submitted to the EPA on June 15, 1983 (Eastman Kodak Company, 1983) and reviewed by the Agency as a part of the

study plan. A copy of this study plan is located in the public record for this test rule (docket no. OPTS-42048D) and is available for inspection in the OPTS Reading Rm., G-004, Northeast Mall, 401 M Street SW., Washington, DC 20460, from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays.

(iii) *Reporting requirements.* (A) The two-generation reproductive effects toxicity test shall be completed and final results submitted to the Agency within 29 months of the effective date of the final Phase II rule.

(B) Interim progress reports shall be provided at 6-month intervals beginning 6 months from the effective date of the final Phase II rule.

(4) \* \* \*

(ii) *Test standards.* The neurotoxicity testing of hydroquinone, consisting of a functional observational battery and neuropathology shall be conducted in accordance with §§ 798.6050 and 798.6400, respectively, of this chapter. The functional-observational battery and the neuropathology assessment may be conducted sequentially on the same group of rats. Neuropathological assessment should begin with the highest dose level and work downward until a no-observable-adverse-effects dose is reached.

(iii) *Reporting requirements.* (A) The neurotoxicity tests shall be completed and final results submitted to the Agency within one year of the effective date of the final Phase II rule.

(B) Interim progress reports shall be provided 6 months from the effective date of the final Phase II rule.

(d) *Effective date.* The effective date of the final Phase II rule for hydroquinone is July 13, 1987.

[FR Doc. 87-12101 Filed 5-27-87; 8:45 am]

BILLING CODE 6560-50-M

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